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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: 16 JUNE 2005

SUBJECT: **DIFENOCONAZOLE** - Exposure/Risk Assessment for the Proposed Use of Difenoconazole on Barley, Cotton and Sweet Corn.

PC Code: 128847 DP Code: 318343 MRID 444908-01

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INTRODUCTION

Under Section 3 of the Federal Insecticide, Fungicide and Rodenticide Act, as amended, the Novartis Crop Protection, Inc., has requested registration of the fungicide difenoconazole for use as a seed treatment (protectant) for barley, cotton and sweet corn. This memorandum serves as the HED's estimates of exposure and risk that might result from the proposed new uses.

USE PATTERN SUMMARY

The product proposed for use is Dividend® Fungicide which is 3.13 lb active ingredient (ai) per gallon liquid (contains 32.8 % difenoconazole). Dividend® is currently a registered product (EPA Reg. No. 100 - 740). The proposed use is as a seed protectant in the process of commercial seed treatment or with the use of commercial grade seed treatment equipment. According to the proposed label it may NOT be used on agricultural establishments in hopper-box, planter-box, slurry-box or other seed-treatment applications at or immediately before planting.

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For barley, the target pests are *Fusarium* and *Cochliobolus spp* root disease organisms. The rate of application ranges from 0.5 - 1.0 fl oz (0.0122 - 0.0244 lb ai)/cwt (hundred lb seed). The same rate of application is proposed for sweet corn seed with the target pest being *Penicillium* spp. For cotton, the range of the application rate is slightly different being 1.0 - 1.25 fl oz (0.0244 - 0.0305 lb ai)/cwt seed. The target pests are *Rhizoctonia* and *Pythium* spp.

There are no personal protective equipment directions on the label. There is a restricted entry interval of 12 hours (to fields planted with treated seed).

OCCUPATIONAL PESTICIDE HANDLER EXPOSURE

Based upon the proposed use pattern and the HED's previous experience with seed treatment and seed treatment materials, HED believes the most highly exposed occupational pesticide handlers in this case are: 1) mixer/operator, 2) bagger and 3) bag sewer. In this regard, Novartis Crop Protection Inc. submitted "An Evaluation of Exposure to Mixer/Operators, Baggers, and Bag Sewers Handling the Active Ingredient Difenoconazole [sic] (Dividend® Twin-Pak™ FUNGICIDE) During Cotton Seed Treatment" (MRID 444908-01). Novartis based its assessment on MRID 4308000-49 "Worker Exposure to Apron Flowable While Treating Seed Commercially". The Novartis assessment was based upon the maximum application rate for cotton (1.25 fl oz/cwt) and toxicological endpoints from a 1995 memorandum by B. Kitchens - "Evaluate New Use of on Farm Seed Treatment for the Active Ingredient Difenoconazole (Dividend 0.15 and 0.31 FS) and Conduct an Exposure Assessment. Novartis assumed 100 % dermal absorption.

On 8 September 1998, the HED Hazard Identification Assessment Review Committee (HIARC) met to discuss the toxicological database relative to difenoconazole (Memo, A. Kocialski, HED DOC No. 012873, "DIFENOCONAZOLE - Report of the Hazard Identification Assessment Review Committee" 25 September 1998). Relative to the assessment herein, the HIARC identified a short-term (1 - 7 days) dermal toxicological endpoint (25 mg a.i./kg bw/day) from a developmental study in the rabbit. The effects seen were post-implantation loss, increased resorption per doe and decreased body weight (maternal effects). The HIARC determined an intermediate-term dermal toxicological endpoint (1.25 mg a.i./kg bw/day) from a 2-generation reproduction study in the rat. The effects seen were decreased pup weights on day 21. The HIARC determined that a 75 % dermal absorption factor should be used since the dermal endpoints were determined from oral studies.

The RAB1 chemical review team has determined that the original determination of short-term duration exposures (1 - 7 days) is applicable to HED's current policy of considering short-term exposure duration as being 1 - 30 days. The original HIARC review did not include inhalation toxicological endpoints. The RAB1 chemical review team has determined that inhalation exposure and risk assessment is necessary and that the short-term and intermediate-term duration inhalation exposures should be assessed using the same toxicological endpoints as were

determined for dermal exposures. For inhalation exposure, HED assumes 100 % absorption.

The Cancer Peer Review Committee (CPRC) has classified difenoconazole as a Group C possible human carcinogen. However, the committee recommended using the MOE approach for assessment (Memo, J.Rowland and E. Rinde, 7/24/94). However, the Agency has not determined an acceptable level of concern using the MOE approach. In addition, exposures are not expected to be chronic exposures. Therefore, a cancer risk assessment is not necessary here.

The HED Science Policy Council for Exposure (ExpoSAC) in conjunction with the Gustoffsen seed treatment company has developed software to facilitate estimation of exposure and risk that result from commercial seed treatment. The software uses HED standard computational practices in conjunction with "unit exposures" derived from a number of seed treatment studies evaluated and accepted by HED. Unit exposures are expressed as mg ai/lb ai handled and are specific to "job" or work activity.

The results from the seed treatment calculator are presented in the following tables, for short- and intermediate-term exposures for each proposed crop seed. The calculator uses the following convention.

a) Label Rate (fl oz/cwt) x concentration (lb ai/gal) ÷ 128 fl oz/gal ÷ 100
b) Unit Exposure (UE) from Standard Operating Procedure for seed treatment (Guidance No. 14, May 1, 2003.
c) Daily Exposure (loaders, sewers, bagger & multiple activities =
[Rate (lb ai/lb seed) x amt seed treated/day x % absorption x UE (mg ai/lb handled) ÷ body weight]
d) Daily Exposure (seed planters) = [Rate (lb ai/lb seed) x lb seed planted/day x % absorption x UE ÷ body weight
e) MOE (unitless) = toxicological endpoint (mg a.i./kg bw/day) ÷ daily exposure (mg a.i./kg bw/day)
f) Combined MOE (unitless) 1/(1/Dermal MOE) + (1/Inhalation MOE)

ESTIMATES OF OCCUPATIONAL PESTICIDE HANDLER EXPOSURE TO DIFENOCONAZOLE FROM COMMERCIAL SEED TREATMENT

V. CALCULATE HANDLER EXPOSURE AND MOE							
Barley short-term	Unit Exposure (UE) mg/lbs.ai [b]		Daily Exposure mg/kg/day [c, d]		Short & Intermediate MOE [e]		Combined MOE [f]
	Dermal	Inhalation	Dermal	Inhalation	Dermal	Inhalation	Dermal & Inhalation
Loader / Applicator:	0.0230	0.00034	0.043266	0.000853	578	29316	567
Sewer:	0.0062	0.00023	0.011663	0.000577	2144	43336	2042
Bagger:	0.0091	0.00016	0.017118	0.000401	1460	62296	1427
Multiple Activities:	0.0420	0.00160	0.079008	0.004013	316	6230	301
Seed Planters:	0.2500	0.00340	0.012445	0.000226	2009	110783	1973

V. CALCULATE HANDLER EXPOSURE AND MOE							
barley intermediate-term	Unit Exposure (UE) mg/lbs.ai [b]		Daily Exposure mg/kg/day [c, d]		Short & Intermediate MOE [e]		Combined MOE [f]
	Dermal	Inhalation	Dermal	Inhalation	Dermal	Inhalation	Dermal & Inhalation
Loader / Applicator:	0.0230	0.00034	0.043266	0.000853	29	1466	28
Sewer:	0.0062	0.00023	0.011663	0.000577	107	2167	102
Bagger:	0.0091	0.00016	0.017118	0.000401	73	3115	71
Multiple Activities:	0.0420	0.00160	0.079008	0.004013	16	311	15
Seed Planters:	0.2500	0.00340	0.012445	0.000226	100	5539	99

V. CALCULATE HANDLER EXPOSURE AND MOE							
Cotton short-term	Unit Exposure (UE) mg/lbs.ai [b]		Daily Exposure mg/kg/day [c, d]		Short & Intermediate MOE [e]		Combined MOE [f]
	Dermal	Inhalation	Dermal	Inhalation	Dermal	Inhalation	Dermal & Inhalation
Loader / Applicator:	0.0230	0.00034	0.012052	0.000238	2074	105243	2034
Sewer:	0.0062	0.00023	0.003249	0.000161	7695	155577	7333
Bagger:	0.0091	0.00016	0.004768	0.000112	5243	223642	5123
Multiple Activities:	0.0420	0.00160	0.022008	0.001118	1136	22364	1081
Seed Planters:	0.2500	0.00340	0.002947	0.000053	8482	467748	8331

V. CALCULATE HANDLER EXPOSURE AND MOE							
Cotton Intermediate-term	Unit Exposure (UE) mg/lbs.ai [b]		Daily Exposure mg/kg/day [c, d]		Short & Intermediate MOE [e]		Combined MOE [f]
	Dermal	Inhalation	Dermal	Inhalation	Dermal	Inhalation	Dermal & Inhalation
Loader / Applicator:	0.0230	0.00034	0.012052	0.000238	104	5262	102
Sewer:	0.0062	0.00023	0.003249	0.000161	385	7779	367
Bagger:	0.0091	0.00016	0.004768	0.000112	262	11182	256
Multiple Activities:	0.0420	0.00160	0.022008	0.001118	57	1118	54
Seed Planters:	0.2500	0.00340	0.002947	0.000053	424	23387	417

V. CALCULATE HANDLER EXPOSURE AND MOE							
Sweet corn short term	Unit Exposure (UE) mg/lbs.ai [b]		Daily Exposure mg/kg/day [c, d]		Short & Intermediate MOE [e]		Combined MOE [f]
	Dermal	Inhalation	Dermal	Inhalation	Dermal	Inhalation	Dermal & Inhalation
Loader / Applicator:	0.0230	0.00034	0.011690	0.000230	2139	108498	2097
Sewer:	0.0062	0.00023	0.003151	0.000156	7933	160389	7559
Bagger:	0.0091	0.00016	0.004625	0.000108	5405	230559	5281
Multiple Activities:	0.0420	0.00160	0.021348	0.001084	1171	23056	1114
Seed Planters:	0.2500	0.00340	0.001965	0.000036	12723	701623	12496

V. CALCULATE HANDLER EXPOSURE AND MOE							
Sweet Corn Intermediate-term	Unit Exposure (UE) mg/lbs.ai [b]		Daily Exposure mg/kg/day [c, d]		Short & Intermediate MOE [e]		Combined MOE [f]
	Dermal	Inhalation	Dermal	Inhalation	Dermal	Inhalation	Dermal & Inhalation
Loader / Applicator:	0.0230	0.00034	0.011690	0.000230	107	5425	105
Sewer:	0.0062	0.00023	0.003151	0.000156	397	8019	378
Bagger:	0.0091	0.00016	0.004625	0.000108	270	11528	264

Multiple Activities:	0.0420	0.00160	0.021348	0.001084	5
Seed Planters:	0.2500	0.00340	0.001965	0.000036	63

For short-term exposures, all MOEs are > 100 and the risks do not exceed HED's level of concern. For intermediate-term duration dermal exposures (1 - 6 months), some MOEs are < 100. For barley: loader/applicator MOE 29
bagger MOE 73
multiple activities MOE 16 (multiple activities are comprised of "odd jobs" such as sweeping/cleaning up at day's end);
For cotton: multiple activities MOE 57
For sweet corn: multiple activities MOE 59.

In order to reduce dermal exposure, workers could be asked to wear additional protective clothing such as coveralls over normal work clothing. However, seed treatment facilities are often very hot during summer months and an additional layer would likely prove more of a problem from heat stress. HED notes that the estimates are based upon a 75 % dermal absorption factor that is derived from an oral study. It is rare indeed that dermal absorption would exceed 50 %. A 75 % dermal absorption factor should be viewed as highly conservative i.e., protective. HED believes it is unlikely that an individual would actually experience intermediate-term exposures. That is to say, it is unlikely that an individual would treat either of the three grains, uninterrupted, for a period of 1 - 6 months. Seed treaters are likely to receive orders for treatment with other materials etc such that it is more likely that a series of short-term duration (1 - 30 days) exposures might occur. Due to the conservative nature of the assessment and the uncertainties involved in the dermal absorption factor, HED does not recommend additional protective factors in this situation.

RESTRICTED ENTRY INTERVAL (REI)

Since the proposed use pattern is for treatment of seed, a restricted entry interval for the proposed uses is not applicable. The label does list a REI of 12 hours for re-entering fields planted with treated seed. Difenoconazole is classified in Acute Toxicity Category III for acute dermal toxicity and primary eye irritation. It is classified in Category IV for acute inhalation toxicity and primary skin irritation. It is not a dermal sensitizer. Therefore, the interim worker protection standard (WPS) REI of 12 hours is adequate to protect workers who might enter fields planted with treated seed.

ATTACHMENT

ACUTE TOXICITY OF DIFENOCONAZQLE

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
81-1	Acute Oral	42090006	LD_{50} =1453 mg/kg	III
81-2	Acute Dermal	42090007	LD_{50} =>2010 mg/kg	III
81-3	Acute Inhalation	42090008	LC_{50} =>3300 mg/m [4 hrs. Exposure]	IV
81-4	Primary Eye Irritation	42090009	mild eye irritation reversible in 7 days	III
81-5	Primary Skin Irritation	42090010	slight irritant	IV
81-6	Dermal Sensitization	42090011 42710004	negative	NA

SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary [females 13+]	NOAEL= 25	post-implantation loss, increased resorption per doe, decreased body weight	developmental rabbit
	UF = 100		
	Acute RfD = 0.25 mg/kg		
Acute Dietary (General Population including infants and children	None	An endpoint attributable to a single exposure (dose) was not available from the oral toxicity studies including the rat and rabbit developmental toxicity studies.	
Chronic Dietary	NOAEL = 0.96	cumulative decreases in body weight gains	chronic/once rat
	UF = 100	**Chronic RfD = 0.01 mg/kg/day**	
Short-Term[a] (Dermal)	oral NOAEL=25	post-implantation loss, increased resorption per doe, decreased body weight	developmental rabbit

Intermediate-Term[a] (Dermal)	oral NOAEL=1.25	based on decreased pup weight on day 21	2-generation reproduction rat
Long-Term (Dermal) Non Cancer	None	Long-term dermal exposure is not expected based on a one time application as a seed treatment. This risk assessment is not required.	
Long-Term Dermal[a] (Cancer)	NOAEL =4.7	Difenoconazole is classified as a Group C, possible human carcinogen with a non-linear (MOE) approach for human risk characterization (CPRC Document, 7/27/94).	
Inhalation Any time period)	None	Based on the low acute toxicity [Toxicity_Category IV] , the application rate [0.5-1.0 fl.oz./100 lbs of seed] the application method [standard slurry or mist-type seed treater] and the number of applications [1x] there is minimal concern for potential inhalation exposure/risk. This risk assessment is not required.	

a =A dermal absorption factor of 75% should be used for route-to-route extrapolation..

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